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A CASE OF GENERAL MILIARY TUBERCULOSIS, WITH AN OPEN FORAMEN OVALE AS A FACTOR IN ITS PRODUCTION.

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The role of a persistent foramen ovale in permitting pieces of thrombi and tumor cells to pass directly from the right auricle to the left side of the heart has been brought into prominence by various investigators. In none of the literature consulted is there mention of the passage of bacteria through such an opening in the interauricular wall. It is our opinion that we have a case in which tubercle bacilli were disseminated through the avenue of an open foramen ovale. Other interesting features of the case now to be described are the extent and size of the tuberculous nodules on the peritoneum and the tuberculous invasion of the pancreas. Though aware of the hypothetical nature of the conclusion regarding the pathogenesis, I feel, from the data, that the inference is highly probable and of great interest in relation to general miliary tuberculosis. Throughout the work I have had the assistance and helpful criticisms of Dr. A. P. Ohlmacher, the director of the pathological laboratory of the Ohio Hospital for Epileptics.

Clinical History. Only the following points have been obtainable: C. E., aged twenty-four years, was a male, colored, an imbecile, and an inmate of the Ohio Hospital for Epileptics for ten years. He had had idiopathic epilepsy for thirteen years. His grand mal attacks occurred principally at night and at irregular periods. His family and previous history were unobtainable, except that until the day before his death he was up and about and that within the last two months of his life he had failed visibly in weight and strength. His physician was called one evening for the reason that during an attack the patient had bitten his tongue severely, almost severing the organ about an inch from the tip. Examination revealed a startling prostration, a temperature of 101°, a weak, irregular pulse of 127, and a respiratory rate of 40 per minute. That the tongue wound could cause the observed signs was not deemed possible, but before enough data could be collected for a diagnosis the patient died. The lethal ending was not attended with status epilepticus nor with any single grand mal attacks.

Gross and Microscopic Morbid Anatomy. The body was fairly well nourished. The anterior inch of the tongue was almost entirely separated from the rest by a deep, gangrenous wound. The oral cavity was otherwise normal. Subcutaneous lymph nodes, except the inguinal, were not palpable, and the latter showed no unusual size. The testicles were of equal size, small, and soft, and presented no nodules to the touch. There was no fluid in the abdominal cavity. The parietal peritoneum adhered to the omentum. The intestines were matted together. All these adhesions could be broken without much difficulty. Both surfaces of the abdominal serosa were studded with an immense number of large, yellowish, confluent, elevated nodules, which were somewhat hard and recalled to mind tumor metastases. The liver and spleen were likewise somewhat firmly bound by the peritoneal exudate to the diaphragm, to the parietal peritoneum, and to the neighboring viscera. The pancreas was practically embedded in the exudate and in a cordon of large glands. The mesenteric lymph nodes were only slightly enlarged. The iliac, the lumbar, the aortic, and especially the cœliac glands were much increased in volume. The anterior and posterior mediastinal glands were much above normal size. There were adhesions in each pleural cavity over the entire lung, which connections were easily broken by the hand. There was no fluid in either pleural sac.

The heart and pericardium together weighed 425 grams. The latter was adherent to the heart all over. On stripping off the pericardium some yellowish nodules were seen. The cardiac orifices and valves were normal. There was a slight hypertrophy of the left ventricle. The musculature of the right auricle was thickened and its endocardium was cloudy and dense. The foramen ovale was open, and a diagonal slit, admitting a one-quarter inch probe and running anteroposteriorly from left to right, made communication between the two auricles. The fossa ovalis was deep and bulged to the left. The ring of Vieussen was well developed and protruding, and was continuous with a thick, pronounced Eustachian valve. Microscopic examination revealed fresh tubercles in the thin exudate on the epicardium. The musculature showed a recent myocarditis, but no tubercles after a search through many sections.

The right lung weighed 930 grams, the left 800 grams. They were similar, of a deep-red color, and crepitated somewhat. The pleura was slightly thickened. Cut surface showed a pale brownish color and numberless whitish tubercles of the size of millet-seeds, which were likewise plainly seen when the pleura was stripped off. Both lungs were searched for old caseated foci, but none was found. At the apices the tubercles were somewhat larger to the eye than in the rest of the lung, a fact which is of interest in view of Hansemann's[1] recent contention that in simple miliary tuberculosis there is no difference; but there were no old lesions, like cavities, fibrous changes, or calcareous deposits. The bronchial glands were large, but were discrete and not soft. Microscopic examination of the lung itself showed many tubercles of small size, in the largest of which there was some breaking down in the centre, but practically all of them were discrete. The lymphoid and epithelioid elements of the tubercles were distinct, but it is noteworthy that giant cells were found in only very few of them. Other characteristics of the lung sections were a moderate dilatation of blood-vessels and many alveoli and bronchi filled with cells, a mucoid substance, and considerable detritus—in short, some of the evidences of bronchopneumonia.

The spleen weighed 440 grams, and was adherent to the diaphragm, the liver, the stomach, and the intestines. At the hilus of the organ there were four or five somewhat enlarged lymph glands. The spleen was large and firm, and, on the capsule, there were numerous large, yellowish, elevated nodules, similar to those on the other peritoneal surfaces. It cut readily and the brown pulp showed no increase of connective tissue but a great abundance of whitish, pinpoint spots universally diffused. Microscopically it was somewhat difficult to differentiate the miliary tubercles at first glance, inasmuch as there were no giant cells present and the Malpighian bodies were numerous. However, on closer study, the epithelioid cell centre and ring of lymphoid cells served to distinguish the tubercles from the Malpighian bodies with their uniform structure of lymphoid cells and the accompanying arteriole. Only here and there were tubercles showing a central degeneration.

The liver weighed 1840 grams, and was bound firmly to a mass formed by the pancreas, the stomach, neighboring parts of the large and small intestines, and some large lymph glands near the cœliac axis, one of which was almost as large as a hen's egg and situated a little to the left of the hilus of the liver, closely associated with the portal vessels. The gall-bladder was in the mass, and one could not say whether the ducts were patent or not, for, owing to these adhesions, the bile could not be squeezed out nor could the ducts be probed. There were no gallstones in the gall-bladder or ducts. The liver was large and firm. There were nodules on its capsule similar to those on the spleen. The organ cut readily and the incised surface showed many whitish tubercles of pinpoint to pinhead size. The markings of the liver were indistinct and there was no congestion. Besides its involvement with the structures in the mass above mentioned, the liver was adherent to the diaphragm, to the spleen, and to the right kidney. In stained sections the liver showed a great number of fresh tubercles; in fact there were more in the liver in any microscopic field than in the lungs. Here, again, it was noted that only a few presented well-formed giant cells, although in the liver sections the greatest number was found. The tubercles were all of approximately the same structure, with practically no central caseation. On the whole the age of the tubercles, judged from their microscopic appearances, must have been about the same in the liver as in the lungs and spleen. The hepatic parenchyma was otherwise about normal. The intercellular connective tissue was prominent, but there was nothing approaching a cirrhosis. There was no abnormal distention of the vascular system.

The left kidney weighed 165 grams. It was large and waxy looking. The capsule stripped with ease and did not tear the parenchyma. The decapsulated surface showed only a slight injection and a few whitish, circumscribed tubercles, some of which were seen on cut section. The cortex was somewhat increased in thickness. The right kidney weighed 150 grams and was similar to its fellow except that on cut section tubercles could be made out more distinctly. Microscopically a few fresh tubercles were seen in the cortex and in the medulla of both kidneys. Here none was found with the typical giant cells of tubercle, although in one there was a large cell with several nuclei. Otherwise the following conditions were found: (*a*) glomerular tufts were much distended; Bowman's capsules were unchanged, but between the tuft and the capsule there was a good deal of detritus, with an occasional cell; (*b*) the epithelium of the renal tubules was cloudy and desquamated; (*c*) considerable vascular dilatation; (*d*) connective tissue was not increased—briefly the changes of an acute diffuse nephritis. Sections were treated for the amyloid reaction, with a negative result.

Both suprarenal capsules were small and hard, but showed no nodules or caseation. Microscopically, besides the usual fatty infiltration, there was noted a pronounced hyperæmia, especially toward the medulla. There was no degeneration of cells. After examining a considerable number of sections, two tubercles were found, one fresh and one with a partial central degeneration, and neither showing a giant cell.

The pancreas weighed 120 grams, and, as mentioned before, was surrounded by enlarged tuberculous glands, and directly upon its head lay the largest of the cœliac glands. Microscopically there was no increase of connective tissue, the gland tubules were unchanged, and the islands of Langerhans were intact and of usual size. One partly caseated tubercle was found in the parenchyma in the lower border and just at the edge. It was entirely within the pancreas, though its outer lymphoid ring extended to the extreme edge of the lower border of the organ. A more prolonged search would probably have demonstrated other tubercles.

The prostate was soft and not enlarged, and microscopic examination disclosed no trace of tuberculosis or other inflammation. The testicles were, by an oversight, not saved, but palpation had revealed no nodules or enlargements of any kind, and both vasa deferentia were, at autopsy, found regular and of their usual consistency.

The peritoneum, as indicated before, exhibited a most striking hyperplastic tuberculosis. The nodules were as large as a bean in many locations, and the whole process was diffuse and confluent. The tumor-like nodules reminded one a good deal of the "Perlsucht" of cattle, and compared favorably with the description of a form of latent tuberculosis of the peritoneum given by Kaufmann.[2] Sections of such nodules showed an extensive caseation, only the periphery containing tissue not degenerated. There were no ulcers in the intestines, which were negative except for a slight increase in lymphoid tissue.

All of the abdominal and thoracic lymph glands presented a great augmentation in size, but a gradual decrease in size of the glands from the abdomen up was noticeable. The largest ones were the lumbar and cœliac. Those in the mediastinum were about the same volume as the bronchial glands. The deep cervical nodes were slightly larger than normal. Unfortunately, nothing further can be said of the inguinal glands except that through the skin they showed no marked increase in size. Microscopically these all revealed an advanced caseation. Those in the cervical region were similarly destroyed, but in them the process could be denoted comparatively recent, for there were many fresh, well-developed tubercles present.

There was a persistent thymus, with imperfectly developed corpuscles of Hassal, but no tuberculosis of that organ was found, though it lay within a mass of tuberculous glands. The thyroid was negative.

The brain weighed 1235 grams. The dura was unchanged. The pia was slightly cloudy over the convexity. Otherwise the encephalon was negative except that there were a few slender adhesions between pia and dura at the base in the region of the circle of Willis and under the frontal lobes. No tubercles could be definitely made out, and, in spite of the basal adhesions, sections of the pia in those regions contained no evidence of tuberculosis. The spinal cord was negative.

Direct smears from the peritoneum and liver showed no acid-resisting bacilli. In those from the lungs and spleen only a few such bacteria were found. Blood-serum inoculations from the spleen, heart's blood, peritoneum, and pia remained sterile. From the lung staphylococcus aureus and albus were isolated. From the liver there was obtained a short, thick bacillus, which reacted in all ways like the colon bacillus, and was probably an artificial contamination.

COMMENTS. In summing up and interpreting the foregoing data, I wish to prove three things: first, that the primary seat of the affection was in the abdominal cavity; second, that the general tuberculosis originated by the lymphogenous route; third, that the open foramen ovale was instrumental in the production of the generalized disease.

It is of prime importance to take some position regarding the original seat of the inflammation. The tuberculosis of the lungs, the liver, the spleen, the kidneys, the suprarenals, the pancreas, and the pericardium was of recent origin, while that of the thoracic and abdominal lymph glands and of the peritoneum was, judging from the size of the nodules and from the extent of the caseation, much older. For these reasons, I assume, and I believe with justification, that the tuberculosis began in the abdomen, and there, no doubt, in the peritoneum, inasmuch as such an affection is not uncommonly primary in the serous covering.

Taking this for granted, under our second heading, the chain of lymph glands from the iliacs up demands some consideration. The lymph nodes around the iliac vessels were considerably larger than usual, the lumbar were still larger, and the cœliac glands were most extreme in size. This increase in volume corresponds with the areas drained by, and with the tributaries of, the groups mentioned. Following up through the thoracic cavity the mediastinal glands were all enlarged, about the size of those in the lumbar region. This chain of glands, I believe, was the path by which the tuberculous material travelled from the peritoneum to the thoracic duct and thence to the heart. This is one of the acknowledged paths for the production of a general miliary tuberculosis, it making no essential difference, as far as result is concerned, whether the tuberculous material breaks through the walls of the thoracic duct or arrives there from its tributaries. This route, first demonstrated by Ponfick, is found especially in tuberculosis of the glands of the abdomen.[3] The thoracic duct was not discoverable in the mass of tuberculous tissue, but the fact that we did not find it is of no importance, for, from the anatomical relations of that vessel to the general glandular system, it was destined to transmit the infectious material.

The possibility of a miliary tuberculosis, consequent to the invasion of a pulmonary bloodvessel, was carefully excluded. Beginning with the arterial and venous trunks, all of the bloodvessels of the lungs down to the smaller ones were carefully slit open in search for a thrombus, an embolus, or an eroded vessel. The result of this dissection was entirely negative. To put this conclusion beyond criticism, sections were cut from the areas where the bronchial glands lay nearest the intima. This examination removed any possible doubt. Nowhere did the tuberculous process approach nearer than the adventitia of the vessel, and, in the majority of cases, a dense connective-tissue ring interposed between the outer coat of the vessel and the degenerative process.

Finally, it is necessary to support our third contention. Having arrived at the right side of the heart, there are possible, because of the presence of the open foramen, two distinct means of dissemination of the tuberculous material. One is by way of the pulmonary artery to the lungs and then back to the left heart and thus to the general circulation, constituting a condition of secondary emboli. Against the assumption that this was the exclusive path, the appended arguments could be brought: (*a*) The lungs in our case do not show any greater invasion than the liver or spleen, which they would have done under the above hypothesis, for tuberculosis is pre-eminently an embolic process.[4] That conditions for embolism and thrombosis are present in capillaries only a few hours after tubercle bacilli arrive in them has been shown recently by Wechsberg[5] and by Miller.[6] All of the organs involved in the acute distribution of the bacilli in our case showed tubercles of about the same age, and though some of the bacteria could undoubtedly escape the lungs and get to the systemic circulation, as careful microscopic work would show, there would not be present, under those conditions, the uniform number of tubercles of the same structure as were found in the lungs, liver, and spleen. (*b*) There would not be present such auspicious conditions in the heart, the details of which have been enumerated and will be further described. (*c*) Such a pulmonary route would probably not be the one in a rapid development of the disease as occurred in our case, evidenced by the lack of giant cells, as indicated by Birch-Hirschfeld,[7] and by the nature of the history of the case. (*d*) Such a path is operative in all cases where tubercle bacilli pass through the pulmonary artery to the lungs, causing miliary tuberculosis there, and yet a systemic invasion of equal grade in all organs is not shown in such instances. The literature has been searched in vain for some specific statement upon the question, not which organs are affected in hæmatogenous miliary tuberculosis when the embolic material passes first to the lungs from the right heart, but whether the intensity and age of the process in the several organs are equal. The table given by Eichhorst[4] (p. 614) and the ones quoted by Birch-Hirschfeld[7] (p. 351) are not to the point. Recently, however, some experiments have been performed by de Haan[8] which give an answer to this question. Assuming, with probability, that there was no open foramen ovale in either of two animals inoculated by de Haan, and to be mentioned here, the conditions of these experiments are just those that I am now discussing and am trying to show to be inadequate to have caused the general miliary tuberculosis of our case. De Haan inoculated tubercle bacilli into the left jugular vein of a horse and of a Javanese beef. At the end of seven weeks, because of great prostration, the horse was killed. The autopsy showed the liver, the spleen, the pericardial sac, and the abdominal cavity to be normal. There were a few tubercles in the kidneys. The lungs, however, were so invaded by tubercles that there was present almost no air-containing tissue. The other animal was killed at the end of nine weeks. It had been affected with the distoma, and the liver presented a corresponding change, but no tuberculosis of that organ is mentioned. The lungs were much involved with miliary tubercles, but the other organs were normal. To the argument that a single introduction of tubercle bacilli invalidates these results for our purpose, it may be stated that in the experiment with the horse a cheesy thrombus remained at the sight of inoculation, which was always a source of further infection. An added proof, the value of which may be questioned, is the work of Strauss and Gamaleia,[9] who injected intravenously a culture of dead tubercle bacilli and found miliary tuberculosis of the lungs, but none of the spleen or liver. (*e*) It appears, from anatomical relations and from the hyperplastic nature of tuberculosis, that the infectious material must get directly into the aortic side to cause a widespread miliary disease and of equal magnitude. Because of all these enumerated facts and arguments, I feel confident that .the general miliary tuberculosis of our case was not produced by way of the pulmonary artery. For the sake of completeness, it might be mentioned that a very improbable explanation of the miliary disease under discussion is by retrograde lymph flow to the organs from the glands into which they drain. It is highly probable that the cervical and, no doubt, the inguinal glands were invaded this way from the thoracic nodes. The age of the process in the former glands is too extreme to have been produced by the route that caused the tuberculosis of the other organs.

The other method of spread and the only other avenue open is by way of the patent foramen ovale. The conditions in our case are exactly those that Rostan[10] and Zahn,[11] who have thoroughly discussed the subject of embolism through an open foramen ovale, call the essentials: a thickened endocardium and an increase in the thickness of the musculature of the right auricle; a well-developed Eustachian valve; thickened and protruding borders of the fossa ovalis; a bulging to the left of the base of the fossa; and an open foramen, which in our specimen admits a quarter-inch probe. The cause that will produce an increase of pressure in the right auricle, so imperatively demanded before there will be a passage through the foramen, was certainly present as a bronchitis, and later as a bronchopneumonia at the first onslaught upon the lungs by the bacilli by way of the pulmonary artery. Rostan says that the bulging of the valve of the opening is a positive proof of such an augmentation of pressure, and Zahn states that, besides this bulging of the fossa to the left, the best anatomical proofs in the right heart of the presence of a stasis and an increase of pressure are the hypertrophy of the muscular walls, the enlargement of the fossa, and the thickening of its edges. Therefore, we have all the requisites for the passage of blood and foreign material from the right auricle to the left, and, though the tuberculosis of the lungs was in large part produced by way of the pulmonary artery, it is highly probable, with such a direct path open, that the production of the general miliary tuberculosis occurred in largest part by way of the open foramen ovale to the aortic side. With the large percentage of such persistent openings in the interauricular wall that is found at autopsy (v. Rostan and Zahn, *loc. cit.*), it is surprising that this route has not been dwelt upon before.

The tuberculosis of the pancreas in our case is of interest only because of its apparent rarity. Most writers dismiss the subject with the statement that it is not often seen. According to some authors, when such a condition is found it exists in a lymph gland on the surface or embedded within the pancreas. Kundrewetzky,[12] however, in 128 cases of consecutive tuberculosis, found 12 positive tuberculous affections of the pancreas, or 9.37 per cent.; in 18 cases of general miliary tuberculosis he found this organ invaded six times, or 33.3 per cent. In children he found 44.44 per cent.

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